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Assessing the impact of non-sucrose IVIG preparations on urinary NGAL levels

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ABSTRACT

Aims: The study aimed to show whether non-sucrose-containing intravenous immunoglobulin (IVIG) administration affected urinary neutrophil gelatinase-associated lipocalin (uNGAL) levels within 24 hours and whether the uNGAL elevations preceded the development of acute kidney injury (AKI).

Methods: The study included 20 patients who received IVIG treatment in internal medicine and neurology clinics between January 2022 and September 2022 and 10 controls (2:1 ratio) with similar age, gender, and comorbidity who did not receive IVIG. The uNGAL levels were classified as elevated (>80 ng/ml) or normal (<80 ng/ml). Patients were monitored for at least 48 hours, up to a maximum of 7 days, or until discharged, to assess the development of AKI.

Results: None of the patients developed AKI during the follow-up period. Posttreatment median uNGAL levels were 7.1 ng/ml (3.35-37.45 ng/ml, p=0.37, Wilcoxon sign-rank test), similar to pretreatment levels. However, when compared categorically, only two patients (10%) had uNGAL levels higher than 80 ng/mL pretreatment, which increased to four patients (20%) posttreatment (p=0.032, Fisher's exact test).

Conclusion: In our small-scale study, although AKI did not develop after IVIG treatment, the increased percentage of patients (increases from %10% to 20) with elevated uNGAL levels suggests that AKI may develop even in formulations that do not contain sucrose as a stabilizer.

Keywords: Acute kidney injury, biomarkers, intravenous immunoglobulin, neutrophil gelatinase-associated lipocalin

INTRODUCTION

Intravenous immunoglobulin G (IVIG) has been used to treat various diseases since it was first administered in 1962.[1] In 1981, the American Food and Drug Administration (FDA) in the United States approved it for patients with immunodeficiency. Over the years, several IVIG preparations have been FDA-approved and have been a cornerstone of treatment for conditions such as multifocal motor neuropathy, chronic B-cell leukemia, immune thrombocytopenic purpura, Kawasaki syndrome, and chronic inflammatory demyelinating neuropathy.[2] As technology has advanced, chemical and enzymatic modifications have allowed for the development of stable monomeric IVIG solutions with concentrations of 4-5% suitable for clinical use.[3] The introduction of modern production techniques led to the widespread use of high-purity and well-tolerated IVIG preparations in the early 1980s.[4] While the pH of IVIG preparations produced by various companies typically falls within the range of 6-7, the optimal pH for stability is between 4 and 4.5. Maintaining a lower pH can help prevent the formation of aggregates more effectively.[5] Additional molecular stabilizers, which include sucrose, maltose, glucose, sorbitol, mannitol, glycine, and proline, are often included in these preparations to enhance stability. However, the inclusion of these stabilizers, particularly sucrose, raises concerns about potential adverse effects; it is believed that acute kidney injury (AKI) associated with IVIG administration may be linked to the lack of sucrase in the kidneys, which is particularly relevant for sucrose, one of the stabilizers utilized.[6]

Early diagnosis of AKI significantly improves the chances of effective treatment. Traditionally, serum creatinine levels and patient urine output monitoring have been used as standard markers to detect AKI. However, serum creatinine levels only begin to rise after the glomeruli's filtration capacity has been reduced by half, and these levels can be influenced by muscle damage and tubule secretion. Additionally, urine output has lower specificity for accurately identifying AKI. Therefore, there is a need for new biomarkers that can be tested in blood

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and urine to diagnose AKI better.[7] One promising biomarker is neutrophil gelatinase-associated lipocalin (NGAL), which can be detected in blood or urine (uNGAL) without any invasive procedures and provides specific responses to kidney damage.[8,9]

In this study, we aimed to demonstrate whether non-sucrose-containing IVIG administration affected uNGAL levels in patients treated with IVIG for various conditions and whether the uNGAL elevations preceded the development of AKI.

METHODS

Ethics approval was from the Maltepe University Clinical Researches Ethics Committee (Date: 15.02.2022, Decision No: 2022/900/15). All participants were informed of the study protocol and provided informed consent. All procedures were carried out by the ethical rules and the principles of the Declaration of Helsinki. The study included 20 patients who received inpatient IVIG treatment in a university hospital's Internal Medicine and Neurology clinics between January 2022 and September 2022 and 10 controls (2:1 ratio) with similar age, gender, and comorbidity distribution who did not receive IVIG. Patients hospitalized for systemic infections, with a recent history of infection or antibiotic use, patients with a current or recent infection with coronavirus (COVID-19), patients with chronic renal failure with eGFR less than 60 mL/min/1.73m^2, and patients with active malignancy were excluded from the study.

Data regarding participant age, gender, and comorbidities were obtained from patient files. Blood and urine samples were collected to measure various levels: serum sodium (mmol/L), potassium (mmol/L), calcium (mg/dl), magnesium (mg/dl), phosphorus (mg/dl), blood urea nitrogen (BUN, mg/dl), estimated glomerular filtration rate (eGFR, calculated by using chronic kidney disease epidemiology collaboration creatinine equation 2021, ml/min/1.73m^2), uric acid (mg/dl), and uNGAL (ng/ml) before and 24 hours after IVIG infusion. Additionally, urine microalbumin and creatinine levels were measured from random urine samples to calculate the urinary microalbumin-to-creatinine ratio, which was used to estimate 24-hour albumin excretion, expressed as mg/day.

The uNGAL levels were classified as elevated (>80 ng/ml) or normal (<80 ng/ml), following literature recommendations that define an optimal cut-off for AKI.[10] The kidney disease: improving global outcomes (KDIGO) criteria were employed to define AKI, characterized by either an increase in serum creatinine of ≥0.3 mg/dl within 48 hours or an increase to ≥1.5 times the baseline within seven days or a urine volume of <0.5 ml/kg/hour for six hours.[11] Patients were monitored for at least 48 hours, up to a maximum of 7 days, or until discharged, to assess the development of AKI.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics 26.0 software (SPSS Inc; Chicago, USA). The conformity of continuous variables to a normal distribution was assessed using Shapiro-Wilk tests. Categorical data were presented as frequencies and percentages, while continuous variables were reported as medians and interquartile ranges. Categorical comparisons were analyzed using Pearson chi-square and Fisher's exact tests. For continuous variables, the Mann-Whitney U test and Kruskal-Wallis's test were used for comparisons. The Spearman correlation test was employed to examine relationships between continuous variables. A statistical significance level of 0.05 was adopted for the study.

RESULTS

The study group consisted of 30 participants, 20 of whom underwent IVIG administration (cases) and ten as controls. Twelve participants (40%) were female, and the median age was 66 years (IQR 53-76). Hypertension was the most prevalent comorbidity with 22 (73.3%) patients, followed by diabetes mellitus with 13 (43.3%) and chronic heart failure with 12 (40%) patients. The least prevalent comorbidity was dyslipidemia, with only 8 (26.7%) patients. Demographic and clinical data of cases and controls are presented in **Table 1**; groups were similar regarding these data.

Table 2 presents the pretreatment laboratory values of cases and controls. The control group had statistically significantly lower calcium levels than cases (p=0.04, Mann-Whitney U test), whereas cases had statistically significantly lower eGFR levels than controls (p=0.015, Mann-Whitney U test). Other laboratory results, including uNGAL levels, were similar between groups. Only one patient from the control group (10%) and two patients from cases (10%) had pretreatment uNGAL levels higher than 80 ng/ml.

None of the patients developed AKI during the follow-up period. Calcium and magnesium levels showed statistically significant changes when cases were compared for pretreatment-posttreatment changes: posttreatment median calcium levels increased to 9.05 mg/dl (8.8-9.35 mg/dl) from a median pretreatment level of 8.5 mg/dl (p=0.006, Wilcoxon sign-rank test), and median magnesium levels increased to 1.97 mg/dl (1.79-2.07 mg/dl) from a median pretreatment level of 1.88 mg/dl. Posttreatment median uNGAL levels were 7.1 ng/ml (3.35-37.45 ng/ml, p=0.37, Wilcoxon sign-rank test), which was similar to pretreatment levels. However, when compared categorically, only two patients (10%) had uNGAL levels higher than 80 ng/ml pretreatment, which increased to four patients (20%) posttreatment (p=0.032, Fisher's exact test).

Both pretreatment and posttreatment uNGAL levels did not show significant differences when compared for age, gender, and comorbidities. Pretreatment uNGAL levels showed a strong positive correlation with microalbuminuria (r=0.49, p=0.006, Spearman's correlation), which was consistent across groups (r=0.77, p=0.009 for controls, r=0.46, p=0.03 for cases, Spearman's correlation). For cases, pretreatment uNGAL levels were also correlated with pretreatment BUN levels (r=0.448, p=0.048) but not with eGFR. Posttreatment uNGAL levels did not significantly correlate with demographic, clinical, and laboratory parameters.

DISCUSSION

AKI following IVIG treatment is believed to result from the added stabilizers to prevent the dimerization and polymerization of immunoglobulins at low pH. Notably, sucrose, a common stabilizer, is associated with approximately 90% of reported AKI cases because sucrase, the enzyme responsible for breaking it down, is not produced in the kidneys. As a result, intravenous sucrose accumulates in the proximal tubule, where it cannot be metabolized. This accumulation leads to the entry of sucrose

Table 1. Demographic and clinical data of case and control groups

		Cases (n=20)	Controls (n=10)	p value
Age		68 (52-76)	62 (54-78)	0.96
Gender	Male	11 (55%)	7 (70%)	
	Female	9 (45%)	3 (30%)	0.35
Comorbidities	Diabetes mellitus	9 (45%)	4 (40%)	0.55
	Hypertension	14 (70%)	8 (80%)	0.45
	Dyslipidemia	6 (30%)	2 (20%)	0.45
	Chronic heart failure	9 (45%)	3 (30%)	0.35

Data were presented as median (IQR), count, and percentages. Data were compared using chi-square and Fisher's exact tests for categorical comparison and the Mann-Whitney U test to compare continuous data of two independent groups.

Table 2. Pretreatment laboratory data of case and control groups

	Cases (n=20)	Controls (n=10)	p value
Sodium (mmol/L)	138 (136-140)	138 (137-139)	0.77
Potassium (mmol/L)	4.13 (3.78-4.5)	4.25 (3.7-4.5)	0.98
Calcium (mg/dl)	9.45 (9.0-9.8)	8.5 (8.1-9.3)	**0.04**
Magnesium (mg/dl)	2.03 (1.88-2.22)	1.88 (1.8-1.96)	0.109
Phosphorus (mg/dl)	3.55 (3.3-4.2)	3.26 (2.86-3.4)	0.08
BUN (mg/dl)	15.4 (12.5-20.9)	16.5 (11-21)	0.55
eGFR (ml/min/1.73 m^2)	82 (70-97)	104 (95-117)	**0.015**
Uric acid (mg/dl)	5.05 (4.55-5.94)	4.75 (3.7-6.5)	0.71
Microalbuminuria (mg/d)	31.6 (15.7-56.7)	29.3 (10.1-157.5)	0.84
uNGAL(ng/ml)	8.5 (2.1-16.2)	18.35 (3.8-63.5)	0.37

Data were presented as median (IQR). Data were compared using the Mann-Whitney U test to compare continuous data of two independent groups. BUN: Blood urea nitrogen, eGFR: Estimated glomerular filtration rate, uNGAL: Neutrophil gelatinase-associated lipocalin

into tubule epithelial cells through pinocytosis, resulting in hyperosmolarity, vacuolization, narrowing of the tubular lumen, and, ultimately, AKI.[6] Herein, we aimed to demonstrate whether non-sucrose-containing IVIG administration was associated with the development of AKI and whether IVIG treatment affected uNGAL levels. In this study, none of the patients developed AKI during the follow-up, possibly due to prior hydration protocols and due to the small scale of the study. Moreover, pretreatment and posttreatment uNGAL levels did not differ significantly. However, in IVIG-treated cases, there was a significant increase in the percentage of cases with uNGAL higher than 80 ng/ml in the posttreatment period, underlying a potential suggestion that non-sucrose stabilizers may also cause renal damage.

NGAL levels serve as a reliable marker for AKI across various age groups and clinical settings, from outpatient care to critical illness.[12] Additionally, NGAL levels are useful in distinguishing between hepatorenal or cardiorenal syndrome and acute tubular necrosis, addressing a significant clinical challenge.[13,14] Apart from being a marker for AKI, the relationship between proteinuria and an increase in NGAL levels is also well-studied.[15] Several studies previously reported that in diabetic patients, NGAL levels increase even before microalbuminuria is present, which carries some potential to be used as a marker for diabetic nephropathy.[16-18] Also, there are studies reporting that NGAL is a potential biomarker for predicting kidney damage earlier that also occurs in the prediabetic stage.[19] Even though it is hypothesized that NGAL levels may have no value in predicting kidney function decline in diabetic nephropathy[20], the marker is still valuable in showing subclinical tubular damage, which other routine clinical markers can't measure. Our study has demonstrated similar results, with pretreatment uNGAL levels showing strong positive correlations with microalbuminuria. However, the lack of correlation in the posttreatment period may underline that other confounding factors have affected the levels of uNGAL, disrupting this correlation. We hypothesize that this may be due to IVIG administration, but due to the small scale of the study, we cannot conclude in this regard. This topic warrants further investigation, with larger-scale studies involving patients using IVIG for different indications and involving patients with no comorbidities that may lead to microalbuminuria, as an increase in uNGAL may also be present prior to the development of proteinuria.

Limitations

Several limitations exist due to the nature of the study. First and foremost, this study has a small sample size, and none of the patients developed AKI due to IVIG treatment. Nevertheless, an increase in the uNGAL level in some patients still underlines the need for further studies to show if non-sucrose IVIG treatment causes tubular damage to some extent. Secondly, this study does not include a subgroup analysis of IVIG indications, which may have impacted the results. Although we aimed to limit the potential confounders by the exclusion criteria, different pathologies that require IVIG treatment may have affected the risk of increased uNGAL levels.

CONCLUSION

AKI can be a significant side effect of IVIG treatment, even in formulations that do not contain sucrose as a stabilizer. In our small-scale study, we found that while none of the patients developed AKI and the median uNGAL levels were similar, however, the percentage of patients with elevated uNGAL levels did increase. This finding highlights the need for further investigation into this issue regarding tubular damage caused by non-sucrose IVIG preparations.

ETHICAL DECLARATIONS

Ethics Committee Approval

Ethics approval was from the Maltepe University Clinical Researches Ethics Committee (Date: 15.02.2022, Decision No: 2022/900/15).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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